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# Hydrolysis of Phosphate Triesters with Copper(II) Catalysts

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Hydrolysis of diethyl 4-nitrophenyl phosphate (DEPNPP) to diethyl phosphate proceeds 1600-fold more rapidly with 1 mM Cu(bpy)$^{2+}$ at pH 6.4 and 75 °C than without metal complex catalyst. Cu(bpy)$^{2+}$ represents Cu(NO$_3$)$_2$ and 2,2′-bipyridine in a 1:1 ratio in aqueous solution. Several Cu(II) complexes may be present under these conditions. These complexes are abbreviated as follows: Cu(bpy)(OH$_2$)$^{2+}$ is Cu(bpy)(OH$_2$)$_4^{2+}$, Cu(bpy)(OH)$^+$ is Cu(bpy)(OH)(OH$_2$)$_3^+$, Cu(bpy)$_2^{2+}$ is Cu(bpy)$_2$(OH$_2$)$_2^{2+}$, and [Cu(bpy)(OH)]$_2^{2+}$ is [Cu(bpy)(OH$_2$)$_2$($\mu$-OH)]$_2^{2+}$. Free copper(II) is abbreviated Cu$^{2+}$. Ideal catalytic behavior was observed for two turnovers after which there was a gradual decrease in the rate of hydrolysis. Since addition of 4-nitrophenolate inhibits catalysis, the decrease in activity can be attributed to product inhibition. The rate exhibited a pH dependence with a kinetic p$K_a$ of 6.9 ± 0.05, close to the first p$K_a$ of Cu(bpy)(OH$_2$)$^{2+}$. On the alkaline pH plateau the rate law was first order in Cu(bpy)$^{2+}$ and DEPNPP. A mechanism where Cu(bpy)(OH)$^+$ binds DEPNPP and bound OH$^-$ attacks phosphorus is proposed. Isotopic labeling studies with $^{18}$OH$_2$ show that P–O cleavage occurs, which is consistent with nucleophilic displacement at phosphorus(V). The Cu(bpy)$^{2+}$-catalyzed hydrolysis of DEPNPP is remarkable because ($p$-NO$_2$C$_6$H$_4$O)(C$_2$H$_5$O)PO$_2^-$ is produced in 14–23% yield in addition to the expected (C$_2$H$_5$O)$_2$PO$_2^-$ product. Since ethanol and 4-nitrophenol differ by 8 p$K_a$ units, one would expect to observe no product derived from ethoxide loss. A mechanism that involves metal- or proton-assisted binding of the alkoxide leaving group is proposed.

## Introduction

The detoxification of phosphorus(V) pesticides and nerve gases is a challenging problem in catalytic hydrolysis chemistry. Divalent metal ions are required in most enzyme-catalyzed nucleophilic displacement reactions at phosphorus(V)[1] and are therefore a logical choice in the search for catalysts to promote hydrolysis of man-made phosphorus(V) toxins. Metal ions have been investigated as catalysts for the hydrolysis of phosphate triesters,[2,3] fluorophosphonates,[4–7] and phosphonates.[8] A few of these hydrolyses are reported to be catalytic in metal complex, yet none have been described past three turnovers of substrate.

As part of our attempt to design metal complexes, which are highly catalytic in the hydrolysis of phosphate esters,[9] we have investigated the mechanism of hydrolysis of diethyl 4-nitrophenyl phosphate DEPNPP by a copper(II) complex. We address the problem of product inhibition, a source of decreasing catalyst efficiency under high-turnover conditions, as a particular problem in the hydrolysis of phosphate triesters. An unexpected insensitivity to the leaving group on phosphorus in the catalyzed reaction is also considered.

## Experimental Section

Reagent grade inorganic salts, and Sigma buffers MES (*N*-morpholineethanesulfonic acid), HEPES (*N*-(2-hydroxyethyl)-piperazine-*N*′-ethanesulfonic acid), EPPS (*N*-(2-hydroxyethyl)-piperazine-*N*′-propanesulfonic acid), and CHES (2-(cyclohexylamino)-ethanesulfonic acid) were purchased from commercial sources and used without purification. The 2,2′-bipyridine ligand was recrystallized twice from hexanes and dried in vacuo. The phosphate triester, diethyl 4-nitrophenyl phosphate, was prepared according to literature methods[10] and distilled in vacuo (~1 Torr at 140–142 °C). The molecular weight calculated from spectrophotometric determination of 4-nitrophenolate on complete acid hydrolysis was 250. A single resonance at −6.09 ppm in D$_2$O was observed by $^{31}$P NMR spectroscopy. All solutions were prepared with Fisher HPLC grade water.

**Table I.** Representative Pseudo-First-Order Rate Constants for the Hydrolysis of Diethyl 4-Nitrophenyl Phosphate to Diethyl Phosphate in Water[a]

| | temp, °C | $10^5k_{\text{obs}}$, s$^{-1}$ | pH |
|---|---|---|---|
| Cu(bpy)$^{2+}$ (1 mM) | 75 | 10 | 6.40 |
| control | 75 | 0.0062 | 6.40 |
| NaOH (1 mM) | 75 | 3.7 | 9.70 |

[a] bpy = 2,2′-bipyridine; $\mu$ = 0.1 M (NaNO$_3$); 0.01 M HEPES; [DEPNPP] = 2.5 mM. $K_w$(75 °C) = $2.0 \times 10^{-13}$.

The concentration of Cu(NO$_3$)$_2$ was determined by titration against ethylenediaminetetraacetic acid with murexide[11] as an indicator. The acid dissociation constant of $p$-nitrophenol at 75 °C was determined to be $2.14 \times 10^{-7}$ by pH titration measurements.

An Orion Research 501 digital ion analyzer, equipped with a temperature compensation probe, was used for pH measurements. All $^{31}$P NMR spectra were recorded with use of a General Electric QE 300-MHz spectrometer. Chemical shifts are reported relative to external 85% phosphoric acid.

**$^{18}$O-Labeling Studies.** A 3-mL 20% $^{18}$OH$_2$ solution 5 mM in diethyl 4-nitrophenyl phosphate and 1 mM in Cu(bpy)$^{2+}$ at pH = 6.5 was heated at 75 °C for 2 h. The solution was diluted to 30 mL and passed through a Sephadex SP-C25 column (Na$^+$ form, 1.5 × 10 cm) to absorb cationic species. The eluant was concentrated to 0.5 mL and analyzed by $^{31}$P NMR spectroscopy. Experiments were duplicated. High-resolution $^{31}$P NMR spectra, for detection of peaks shifted from $^{18}$O incorporation, were recorded with a sweep width of 1000 Hz and were modified by a double exponential multiplier of 6 containing Gaussian multiplier and negative line-broadening components (QE 300 Charm software).

**Product Analysis.** Products of DEPNPP hydrolyses were analyzed by $^{31}$P NMR spectroscopy on complete and partial hydrolysis. Solutions were treated as described above to remove copper catalyst before NMR analysis.

**Kinetics.** The initial rate of production of $p$-nitrophenolate was monitored spectrophotometrically at 400 nm with use of an IBM 9420 UV-Vis spectrometer equipped with a thermostated cell compartment. Reactions performed at pH < 9 were corrected for the degree of ionization of $p$-nitrophenolate at 75 °C. Sigma biological blood buffers (MES, HEPES, EPPS, CHES) were used to maintain a constant pH in the range 6.0–9.0. The pH of solutions was adjusted with NaOH or HNO$_3$ and checked at 75 °C.

First-order rate constants were calculated from the slopes of the linear plots of optical density against time by converting to concentration units

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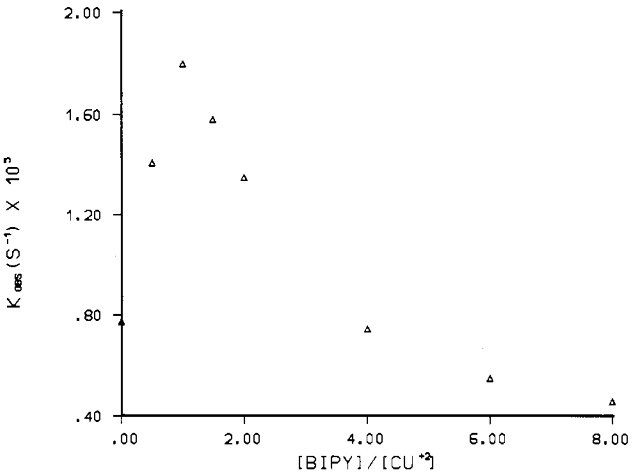


**Figure 1.** Dependence of $k_{obs}$ for the hydrolysis of diethyl 4-nitrophenyl phosphate to diethyl phosphate on the 2,2′-bipyridine to copper(II) ratio in water at 75 °C, $\mu$ = 0.1 M ($NaNO_3$), pH = 7.5, 0.01 M HEPES, [DEPNPP] = 2.5 mM, and $[Cu(NO_3)_2] = 5 \times 10^{-5}$ M.

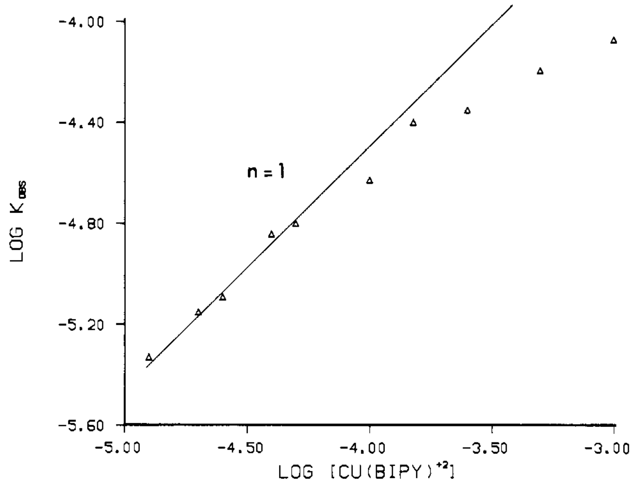


**Figure 2.** Dependence of $k_{obs}$ for the hydrolysis of diethyl 4-nitrophenyl phosphate to diethyl phosphate on catalyst concentration at $\mu$ = 0.1 M ($NaNO_3$), pH = 7.5, and [DEPNPP] = 2.5 mM, showing a first-order dependence on $Cu(bpy)^{2+}$ at low concentrations of catalyst ($<10^{-4}$ M). By use of the first five points, a slope of 0.97 and a correlation coefficient of 0.994 were calculated.

**Table II.** Apparent Second-Order Rate Constants for the Hydrolysis of Diethyl 4-Nitrophenyl Phosphate to Diethyl Phosphate in Water at 25 °C[a]

| catalyst | $10^2k_2$, $M^{-1}$ $s^{-1}$ |
|---|---|
| $Cu(bpy)^{2+}$ [b] | 1.5 |
| NaOH[c] | 0.58 |

[a] bpy = 2,2′-bipyridine; $\mu$ = 0.1 M ($NaNO_3$); 0.01 M HEPES; [DEPNPP] = 2.5 mM. [b] pH = 8.00, based on $Cu(bpy)^{2+}$ concentrations (5–1) $\times 10^{-5}$ M. [c] Based on [NaOH] = $5 \times 10^{-4}$, $1 \times 10^{-3}$, $2 \times 10^{-3}$, and $1 \times 10^{-2}$ M.

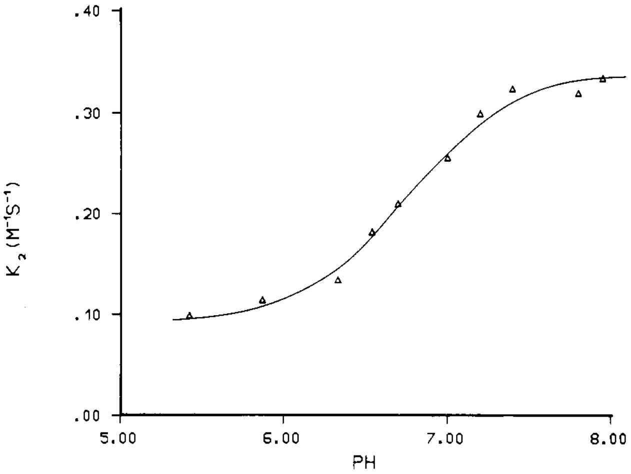


**Figure 3.** Dependence of second-order rate constant, $k_2$, on pH for the hydrolysis of diethyl 4-nitrophenyl phosphate to diethyl phosphate by $Cu(bpy)^{2+}$ in water at 75 °C, $\mu$ = 0.1 M ($NaNO_3$), and [DEPNPP] = 2.5 mM. The data are fit to a theoretical curve with $pK_a = 6.9 \pm 0.05$, $k = 0.075 \pm 0.005$ $M^{-1}$ $s^{-1}$, and $k_1 = 0.36 \pm 0.03$ $M^{-1}$ $s^{-1}$.

($\epsilon$ = 18 700) and dividing by the initial phosphate ester concentration. All experiments were run in duplicate or triplicate, and tabulated data represent the average of these experiments. Standard deviations were in the range 2–5%. Error in rate constants was conservatively estimated from the uncertainties introduced by temperature, pH, and stock concentration fluctuations, since the least-squares fitting error for individual rate experiments was usually negligible. Generally, second-order rate constants were obtained from plots of first-order rate constants against catalyst concentration. Rates of hydrolysis of phosphate esters in the absence of catalyst were measured and, when not negligible, were subtracted from the rate of catalytic hydrolysis.

## Results

Representative pseudo-first-order rate constants are tabulated for the hydrolysis of DEPNPP in water by $Cu(bpy)^{2+}$ and NaOH at 75 °C (Table I). The hydrolysis of DEPNPP at pH = 6.4 in 0.01 M buffer at 75 °C is also provided for comparison. Hydrolysis of DEPNPP by $Cu(bpy)^{2+}$ at 25 °C can be be observed at optimal pH (8.00). Second-order rate constants for the hydrolysis of DEPNPP by $Cu(bpy)^{2+}$ and by NaOH are tabulated (Table II).

The observation of pseudo-zeroth-order kinetics for one turnover of $Cu(bpy)^{2+}$ in buffered solutions containing an excess of phosphate triester confirmed that the copper complex was functioning catalytically. Although up to 30 turnovers were observed, the rate of hydrolysis began to decrease after two turnovers. Addition of diethyl phosphate or ethanol in excess over DEPNPP did not inhibit hydrolysis of DEPNPP; however, addition of a 4-fold excess of 4-nitrophenolate over catalyst substantially inhibited hydrolysis of DEPNPP.

The copper complexes in the rate law of eq 1 are present in an aqueous solution of $Cu^{2+}$ and 2,2′-bipyridine in a 1:1 ratio and may contribute to hydrolysis of DEPNPP. Abbreviations for the

$$k_{obs} = k_1[Cu^{2+}] + k_2[Cu(bpy)(OH_2)^{2+}] + k_3[Cu(bpy)(OH)^+] + k_4[Cu(bpy)_2{}^{2+}] + k_5[[Cu(bpy)(OH)]_2{}^{2+}] \quad (1)$$

copper species involved are defined in the abstract. That the rate of hydrolysis tracks the concentration of $Cu(bpy)(OH)^+$ in solution (Figure 1) suggests that $Cu(bpy)_2{}^{2+}$ does not promote hydrolysis of DEPNPP. The concentrations of these copper complexes[12] at

**Table III.** Effect of Varying 2,2′-Bipyridine to Copper(II) Ratio on Concentrations of Copper(II) Complexes (M) in Water at 75 °C[a]

| $[bpy]_T$ | [bpy] | $[Cu^{2+}]$ | $[Cu(bpy)(OH_2)^{2+}]$ | $[Cu(bpy)_2{}^{2+}]$ | $[Cu(bpy)(OH)^+]$ | $[[(Cu(bpy)(OH)]_2{}^{2+}]$ |
|---|---|---|---|---|---|---|
| $2.5 \times 10^{-5}$ | $7.0 \times 10^{-12}$ | $2.5 \times 10^{-5}$ | $3.2 \times 10^{-6}$ | $4.9 \times 10^{-9}$ | $8.7 \times 10^{-6}$ | $6.5 \times 10^{-6}$ |
| $5.0 \times 10^{-5}$ | $2.6 \times 10^{-10}$ | $1.0 \times 10^{-6}$ | $4.8 \times 10^{-6}$ | $2.8 \times 10^{-7}$ | $1.3 \times 10^{-5}$ | $1.5 \times 10^{-5}$ |
| $1.0 \times 10^{-4}$ | $1.3 \times 10^{-8}$ | $1.7 \times 10^{-8}$ | $4.1 \times 10^{-6}$ | $1.2 \times 10^{-5}$ | $1.1 \times 10^{-5}$ | $1.1 \times 10^{-5}$ |
| $2.0 \times 10^{-4}$ | $4.4 \times 10^{-8}$ | $3.7 \times 10^{-9}$ | $2.9 \times 10^{-6}$ | $2.8 \times 10^{-5}$ | $8.0 \times 10^{-6}$ | $5.5 \times 10^{-6}$ |

[a] bpy = 2,2′-bipyridine; $[bpy]_T$ is the stoichiometric concentration of bpy added; all other columns refer to calculated equilibrium concentrations. $\mu$ = 0.1 M ($NaNO_3$); $[Cu(NO_3)_2] = 5 \times 10^{-5}$ M; pH 7.50. Equilibrium constants were taken from ref 13 and 20.

**Table IV.** Product Composition from the Hydrolysis of Diethyl 4-Nitrophenyl Phosphate in Water at 75 °C[a]

| catalyst | pH | DEP:EPNPP[b] |
|---|---|---|
| $Cu(bpy)^{2+}$ | 6.4 | 3.6 |
| $Cu(bpy)^{2+}$ | 7.5 | 7.2 |
| NaOH | 12 | 17 |

[a] bpy = 2,2'-bipyridine; $\mu$ = 0.1 M ($NaNO_3$); 0.01 M HEPES; $Cu(bpy)^{2+}$ concentration was 1 mM. [b] DEP = diethyl phosphate; EPNPP = ethyl 4-nitrophenyl phosphate; ratio determined by $^{31}P$ NMR spectroscopy. $K_w(75\ °C) = 2.0 \times 10^{-13}$. Hydrolysis of EPNPP was not significant during the reaction times used to measure the ratio.

various 2,2'-bipyridine to copper ratios are listed in Table III. At a 1:1 ratio of $Cu^{2+}$ to 2,2'-bipyridine ($5 \times 10^{-5}$ M, pH = 7.50) hydrolysis of DEPNPP by $Cu^{2+}$ ($k_1 = 0.16$ $M^{-1}$ $s^{-1}$) or by $Cu(bpy)(OH_2)^{2+}$ ($k_2 = 7.5 \times 10^{-2}$ $M^{-1}$ $s^{-1}$; see below) is insignificant (≤2% of the observed rate of hydrolysis).

The rate of hydrolysis of DEPNPP shows a first-order dependence on $Cu(bpy)^{2+}$ concentration at low concentrations of complex (Figure 2). At concentrations greater than $5 \times 10^{-5}$ M the reaction order in $Cu(bpy)^{2+}$ decreases below 1. This parallels the known dimerization[13,14] to the hydroxy-bridged dimer $[Cu(bpy)(OH)]_2^{2+}$ and is consistent with the dimer being inactive as catalyst.

The pH profile (Figure 3) of $Cu(bpy)^{2+}$-catalyzed hydrolysis of DEPNPP, which involves loss of $OC_6H_4NO_2^-$, shows two pH-independent plateaus and an intermediate pH range where the rate of hydrolysis depends on pH. The data can be fit to an expression for the hydrolysis of DEPNPP by $Cu(bpy)(OH_2)^{2+}$ and $Cu(bpy)(OH)^+$ as in eq 2 and 3, where $Cu(bpy)_T^{2+}$ is the total

$$k_{obs} = k_2[Cu(bpy)(OH_2)^{2+}] + k_3[Cu(bpy)(OH)^+] \qquad (2)$$

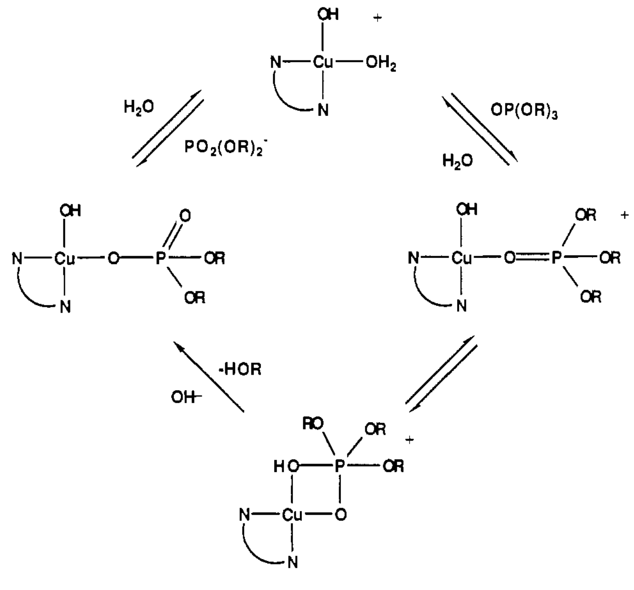
$$k_{obs} = \left[\frac{k_2[H^+] + k_3K_a}{[H^+] + K_a}\right][Cu(bpy)^{2+}]_T \qquad (3)$$

concentration of copper complex, $K_a$ is the dissociation constant for the coordinated water molecule, $k_3$ is the second-order rate constant for $Cu(bpy)(OH)^+$-mediated hydrolysis of DEPNPP, and $k_2$ is the second-order rate constant for $Cu(bpy)(OH_2)^{2+}$-mediated hydrolysis of DEPNPP. A least-squares fitting of the data[15] gave $pK_a = 6.9 \pm 0.05$, $k_2 = 0.075$ (±0.005) $M^{-1}$ $s^{-1}$, and $k_3 = 0.36$ (±0.03) $M^{-1}$ $s^{-1}$.

A few $Cu(bpy)^{2+}$-catalyzed hydrolyses of DEPNPP were monitored periodically by removal of catalyst and analysis by $^{31}P$ NMR spectroscopy. Analysis of hydrolysis experiments at pH 6.4 or pH 7.5, stopped before 1 equiv of 4-nitrophenolate was produced, showed resonances attributed to diethyl phosphate (DEP) and ethyl 4-nitrophenyl phosphate (EPNPP) (Table IV). Note that the rate constants from the spectrophotometric kinetics experiments for the appearance of $OC_6H_4NO_2^-$ are valid, since their determination is not affected by competing hydrolysis to liberate $OEt^-$. Analysis of solutions hydrolyzed over longer time periods showed both diethyl phosphate and ethyl phosphate present in similar proportions. The hydrolysis of ethyl 4-nitrophenyl phosphate by $Cu(bpy)^{2+}$ is ca. 30-fold slower than that of DEPNPP. Under the experimental conditions of excess DEPNPP to catalyst, hydrolysis of the phosphate diester makes a negligible contribution to 4-nitrophenolate production for the data reported in Table IV.

Isotopic labeling experiments were performed to determine whether hydrolysis occurred by C–O or by P–O bond cleavage. Hydrolysis of DEPNPP by $Cu(bpy)^{2+}$ in 17% $^{18}OH_2$ at pH 6.4 was allowed to go to completion, and products were analyzed by $^{31}P$ NMR spectroscopy. The NMR peak assigned to diethyl phosphate showed a satellite peak 0.020 ppm upfield that was 19 ± 3% of the total diethyl phosphate product. Similarly, the $^{31}P$ NMR peak assigned to ethyl 4-nitrophenyl phosphate showed a satellite peak 0.027 ppm upfield, integrating to 20 ± 5% of the total ethyl 4-nitrophenyl phosphate product. The magnitude and direction of this shift resemble those found in other $^{18}O$-labeled phosphate esters.[16] Thus, hydrolysis of both the OEt and $OC_6H_4NO_2$ groups occurs predominantly by P–O bond cleavage.

**Scheme I**



## Discussion

Hydrolysis of DEPNPP proceeds 1600-fold more rapidly with 1 mM $Cu(bpy)^{2+}$ (pH 6.4, 75 °C) than without catalyst (Table I). Since the rate of the control hydrolysis increases with pH faster than the $Cu(bpy)^{2+}$-catalyzed hydrolysis, optimal rate enhancements are obtained at acidic pH. The $Cu(bpy)^{2+}$-catalyzed hydrolysis of DEPNPP, readily observed at room temperature, can also be compared to hydrolysis of the triester by NaOH. Comparison of apparent second-order rate constants for the hydrolysis of DEPNPP establishes that $Cu(bpy)^{2+}$ is a more effective hydrolytic agent at mildly alkaline pH than is NaOH (Table II).

Careful examination of the catalytic properties of $Cu(bpy)^{2+}$ showed ideal catalytic behavior for two turnovers followed by a gradual decrease in the rate of hydrolysis. We were surprised to find that 4-nitrophenolate inhibits hydrolysis of DEPNPP, since hydrolysis of bis(4-nitrophenyl) phosphate by $Cu(bpy)^{2+}$ exhibited ideal catalytic behavior to 1000 turnovers.[9] Presumably, phosphate diesters are better ligands than a phosphate triester, and their hydrolysis is not as easily inhibited. This may be a general phenomenon in the metal ion promoted hydrolysis of phosphate triesters, and it is noteworthy that no more than three turnovers have been reported in any previous studies of the hydrolysis of phosphate triesters by metal complexes.

The mechanism proposed in Scheme I accords with the pH–rate profile, the first-order dependence on $Cu(bpy)^{2+}$ (at ≤$5 \times 10^{-5}$ M) and phosphate triester,[17] and the $^{18}O$-labeling studies. In this scheme, only the mechanism of hydrolysis at alkaline pH is shown. A five-coordinate phosphorane intermediate is proposed in analogy to the mechanism of base hydrolysis of organic phosphate esters; however, we cannot exclude a concerted mechanism.

A Cu–OH moiety or its kinetic equivalent is implicated as the active catalyst at alkaline pH by the pH–rate profile (Figure 3) with an apparent $pK_a$ of 6.9. The $pK_a$ of $Cu(bpy)(OH)_2^{2+}$ measured by potentiometric titration (7.1)[13] is somewhat uncertain

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(12) Equilibrium constants were calculated at 75 °C from data in ref 13 and 20.

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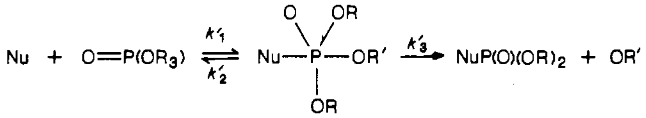
(17) Supplementary kinetic data.

because of the competing dimerization of $Cu(bpy)(OH)^+$. Surprisingly, the hydrolysis of DEPNPP by $Cu(bpy)(OH)_2{}^{2+}$ is only 5 times less effective than hydrolysis by $Cu(bpy)(OH)^+$. Hydrolysis of a phosphate triester by hydroxide nucleophile is $(7 \times 10^6)$-fold more effective than hydrolysis by water nucleophile in the absence of metal ion catalysts. Coordination of the phosphate ester greatly increases its reactivity and presumably decreases its preference for the coordinated hydroxide nucleophile as compared to coordinated water. Also, the hydroxide nucleophile may experience a greater decrease in nucleophilicity on binding to $Cu^{2+}$ than water. This appears to be a general characteristic of $Cu(bpy)^{2+}$-promoted hydrolysis of phosphate esters, as the rate of phosphate diester hydrolysis by $Cu(bpy)^{2+}$ at acidic pH is only 5 times slower than at alkaline pH.[9]

A bifunctional role is proposed (Scheme I) for $Cu(bpy)(OH)^+$ in the catalytic hydrolysis of DEPNPP, since neither nucleophilic attack of Cu–OH on phosphate triester nor electrophilic activation of phosphate triester alone can account for the experimental observations. Comparison of rate constants (Tables I and II) shows that $Cu(bpy)(OH)^+$ is comparable to NaOH as a hydrolytic agent, although the $pK_a$ of the copper complex is some 8 orders of magnitude less than that of hydroxide. Hydrolysis of free DEPNPP by nucleophilic attack of copper hydroxide is thus improbable, and hydrolysis by $Cu(bpy)^{2+}$ (Figure 3) must also involve electrophilic activation of the phosphate triester by complexation. The low selectivity of DEPNPP hydrolyses catalyzed by $Cu(bpy)^{2+}$ toward the $OH^-$ or $H_2O$ nucleophiles also suggest a major role for electrophilic activation of the phosphate triester.

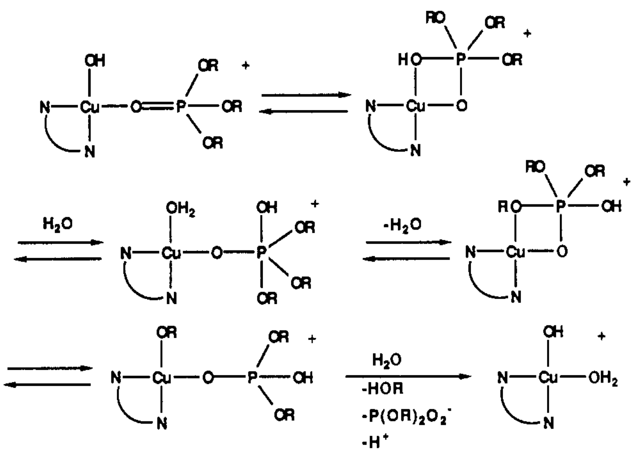
The $Cu(bpy)^{2+}$-catalyzed hydrolysis of DEPNPP is remarkable because $(NO_2PhO)(EtO)PO_2{}^-$ forms in large quantities in addition to the expected product $(EtO)_2PO_2{}^-$ (Table IV). This implies only a slight dependence of the hydrolysis rate on leaving group, since the difference between ethanol and 4-nitrophenol spans more than 8 $pK_a$ units. By contrast, the $Cu^{2+}$-catalyzed hydrolysis of phosphate diesters, such as $P(OEt)(O\text{-}4\text{-}C_6H_4NO_2)O_2{}^-$, shows a strong leaving-group dependence.[9] A similar enhancement of the unexpected hydrolysis product phenyl 4-nitrophenyl phosphate was observed by Gellman, Petter, and Breslow for the hydrolysis of diphenyl 4-nitrophenyl phosphate by a zinc complex and attributed to inhibition of pseudorotation of a five-coordinate metallaphosphorane intermediate.[2] Khan and Kirby[18] have suggested that the small dependence of the rate of hydrolysis of phosphate triesters on leaving-group $pK_a$, when strong nucleophiles are used, may be interpreted by the rate-determining formation of a five-coordinate intermediate, eq 4 ($k'_2 << k'_3$). Decomposition of



$$\mathrm{Nu} + \mathrm{O{=}P(OR_3)} \underset{k'_2}{\overset{k'_1}{\rightleftharpoons}} \mathrm{Nu{-}\overset{O\ \ OR}{\underset{OR}{P}}{-}OR'} \xrightarrow{k'_3} \mathrm{NuP(O)(OR)_2} + \mathrm{OR'} \quad (4)$$

the five-coordinate intermediate becomes rate determining for weak nucleophiles, which results in a larger leaving-group $pK_a$ dependence. This explanation would not apply to our system, since $Cu(bpy)^{2+}$-promoted hydrolyses of DEPNPP exhibit a higher product selectivity ratio with the stronger nucleophile Cu–OH than with $Cu\text{–}OH_2$.

**Scheme II**



One alternative mechanism we propose for the unusual leaving-group dependence (Scheme II)[19] follows from a consideration of the microscopic reverse of Scheme I. Since Cu–OH transfer to bound DEPNPP represents the path by which a nucleophile approaches phosphorus, then perhaps the departing $OEt^-$ or $OC_6H_4NO_2{}^-$ group leaves by the same path as shown in Scheme II. This follows from the principle of microscopic reversibility if one regards $OH^-$ and $OR^-$ as mechanistically equivalent. Therefore, it is the leveling effect of $Cu^{2+}$ assisting departure of the $OR^-$ leaving group that results in the diminished leaving-group effect. The observation (Table IV) of decreased selectivity at a decreased pH may reflect acid catalysis of metallaphosphorane ring opening between species with different OR groups bound to Cu(II) in the mixed ester. The absence of a similar leveling effect in diester hydrolysis[9] could reflect the presence of a more basic $-O^-$ group in the metallaphosphorane intermediate, which could protonate in preference to the groups linking $Cu^{2+}$ and P. An alternative explanation for the pH effect might involve proton (or metal ion) attack at the leaving $OR^-$ group.

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**Supplementary Material Available:** Tables of rate constants for hydrolysis of phosphate triesters with copper(II) catalysts (2 pages). Ordering information is given on any current masthead page.

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(18) Khan, S. A.; Kirby, A. J. *J. Chem. Soc. B* **1970**, 1172–1182.

(19) Scheme II considers only the equilibria under basic conditions for the sake of brevity.

(20) Martell, A. E.; Smith, R. M. *Critical Stability Constants*; Plenum Press: New York, 1974.